



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, DC 20231  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09 448,613	11/22/1999	PAUL B. MCCRAY JR.	IOWA:022	5238

7590 07/18/2002

STEVEN L. HIGHLANDER  
FULBRIGHT & JAWORSKI LLP  
600 CONGRESS AVENUE  
SUITE 2400  
Austin, TX 78701

EXAMINER

SCHINIZER, RICHARD A

ART UNIT	PAPER NUMBER
----------	--------------

1635

DATE MAILED: 07/18/2002

17

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/448,613

Applicant(s)

PAUL MCCRAY ET AL.

Examiner

Richard Schnizer

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☐ Responsive to communication(s) filed on 18 March 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☐ Claim(s) 1-8, 10-39, 41-44 and 46-70 is/are pending in the application.
- 4a) Of the above claim(s) 13-25 and 57-62 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 1-8, 10, 11, 12, 26-39, 41-44, 46-56, 60 and 63-70 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s) \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

Art Unit: 1635

**DETAILED ACTION**

An amendment and supplemental IDS were received and entered as Paper Nos. 14 and 15, respectively, on 3/18/02. Claims 9, 40, and 45 were canceled as requested. Claims 1-8, 10-39, 41-44, and 46-70 remain pending in the application. Claims 13-25, 57-59, 61, and 62 were withdrawn from further consideration in Paper No. 10 pursuant to 37 CFR 1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 9. Claims 1-8, 10-12, 26-39, 31-44, 46-56, 60, and 63-70, and the elected species of retrovirus; membrane channel; cystic fibrosis; and the combination of a hypotonic solution and a chelator, are under consideration in this Office Action.

***Rejections Withdrawn***

K.T.  
6/17 The rejections under 35 USC 112, second paragraph of claims <sup>1-8, 10-12,</sup> ~~1-12~~, 32, 33, 48-52, and 68-70 are withdrawn in view of Applicants amendments and arguments.

The rejections under 35 USC 102 of claims 38, 43 and 68-70 are withdrawn in view of Applicants amendments and arguments.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

Art Unit: 1635

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 10-12, 26-39, 31-44, 46-56, 60, and 63-70 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record in Paper No. 10.

The instant invention is directed to improving the efficiency of gene transfer to epithelial cells by increasing the transepithelial permeability of the epithelial sheet. Recent publications, as well as the specification, indicate that receptors for adenovirus, adeno-associated virus, and retroviruses tend to be sequestered on the basolateral surface of the lung epithelial cells, and are therefore not available to bind viruses delivered via the lumen of the lung. The essence of the instant invention is two provide access to these receptors by either allowing viruses to penetrate the epithelium and associate with its basolateral surface, or by causing redistribution of the receptors to the apical surface of the epithelium, which is exposed to the lumen of the lung.

The specification discloses no use for the elected methods and compositions other than the treatment of disease, and the only readily apparent use other than disease treatment is in the process of developing such treatments. Thus, in order to enable the elected methods and compositions, the specification must teach how to treat CF by administration to epithelial cells *in*

Art Unit: 1635

*vivo* of a retroviral vector encoding a membrane channel, wherein the permeability of the epithelial tissue is increased by treatment with a hypotonic solution and EGTA.

The specification fails to enable the elected invention for the reasons set forth in Paper No. 10, reiterated below.

The state of the art of CFTR gene therapy is highly unpredictable. Successful treatment of cystic fibrosis by gene therapy had not been accomplished as of the time of filing due to several factors. First, there is a lack of information regarding the appropriate target cells for gene delivery. See Rosenfeld and Collins (1996). If gene transfer to the apical surface of the epithelium is required, this transfer is impeded by surface fluid, cilia, and mucus. If transfer to the submucosal glands is required, then systemic delivery is indicated. See Rosenecker (1998). The specification fails to address systemic delivery in the treatment of CF, focusing instead on luminal delivery. Because it is unknown what cell types need to be transfected in order to treat CF, it is also unclear how many cells must be transfected and what profile of gene expression is required in order to achieve therapy. See e.g. Rosenfeld and Collins (1996, first full paragraph of column 1 on page 243); Boucher (TIG 1.2(3): 81-84, 1996, page 81, paragraph bridging columns 2 and 3); Alton and Geddes (J. R. Soc. Med 90 Suppl 31: 43-46 1997); Davies (Mol. Med Today 4(7): 292-299, 7/1998, page 294, column 2, lines 20-28); Boucher (J. Clin. Invest. 103(4): 441-445 2/1999); and Flotte (Chest 120: 124S-131S, 2001, page 124S, column 2 second full paragraph). Also, the expression profile of CFTR *in vivo* is extraordinarily complicated, so even if a therapeutic expression profile was known, due to the current inadequate

Art Unit: 1635

state of the art in vector targeting and gene expression control, delivery of CFTR in vivo is expected to result in ectopic and unregulated expression of CFTR. See Wilson (1995). The level of expression required for therapy is also unknown because the relationship between abnormal ion transport and pathophysiology of CF is incompletely understood. Briefly, the molecular problem responsible for CF is a defect in a chloride ion transporter known as CFTR. One hypothetical explanation for the progress of the disease depends on a failure to transport chloride ions, leading to abnormal absorption of sodium ions by the epithelium. This leads to dehydration and thickening of the mucus in the lungs, which in turn leads to a variety of pathophysiological outcomes including inflammation, repeated infections, and decreasing pulmonary function. Alternatively, the defect in CFTR could somehow affect the actual composition of mucus in the lung, resulting in the recognized pathologies. See Wilson (1995) paragraph bridging pages 2547 and 2548. Thus a primary focus of treatment is the restoration of chloride ion transport. Boucher (1999) teaches that it is likely that the percentage of epithelial cells requiring functional correction to restore normal chloride ion transfer in vivo may well exceed 10%, and advises that the simplest strategy to assure efficacy is to mimic the normal pattern of in vivo expression by achieving gene expression in 100% of lung epithelial cells. See paragraph bridging pages 441 and 442, page 442 column 1, lines 25-30, and 42-45. Boucher concludes that a one or two order of magnitude increase in vivo gene transfer efficiency, above that observed in clinical trials, will be required for therapeutic relevance in CF treatment. See page 444, column 2, first sentence of second full paragraph. Clinical studies have shown success in partially correcting chloride ion

Art Unit: 1635

transport, however Alton and Geddes (1997) teach that it is unknown whether the chloride or sodium defect associated with CF is the more important error to correct, and that the degree of correction needed for clinical benefit of these defects is unknown. See page 45, lines 7-10 of first full paragraph. Furthermore, Davies (1998) teaches that if normalization of sodium ion transport is required for therapeutic effect, then the levels of gene transfer observed to date will be inadequate because correction of sodium ion transport has not been achieved in the majority of preclinical and clinical studies. See page 294, column 2, lines 22-28. Rosenfeld (1996) indicates that although restoration of chloride conductance in monolayer cells is achieved by transfection of 5-7% of the cells, normalization of sodium ion reabsorption will require transfection of a much higher percentage of cells. See page 243, column 1, lines 15-18.

For these reasons it was apparent at the time of the invention that the practice of gene therapy of CF was highly unpredictable. Shortly after the application was filed, Boucher (1999) summarized the state of the art by stating that "despite an impressive amount of research in this area, there is little evidence to suggest that an effective gene transfer approach for the treatment of CF lung disease is imminent."

Against this background, the specification teaches working examples in which normal rabbit lungs were treated with EGTA in vivo in order to either permeabilize the epithelium, or cause receptor redistribution, prior to infection with retroviral vectors. From 2.5% to 4.8% percent of rabbit lung epithelial cells were transfected. See page 73, lines 19-26, and page 74, lines 10-12, and 25-27. However, the teachings of the those of skill in the art at the time of the

Art Unit: 1635

invention indicate that transfection of at least 6-10% of epithelial cells would be required in order to restore normal chloride ion transport in vivo. See Johnson et al (of record C40). However, as Noted by Boucher (1999), this estimate is based on in vitro assays using monolayer epithelial cells which were highly connected by gap junctions. This allows chloride ions from over-corrected cells to diffuse to uncorrected cells. Boucher indicates that it is likely that the number of gap junctions in vivo is less than that in the in vitro monolayer model, so the minimum number of cells which must be transfected in vivo may well exceed 10%. See page 442, column 1, lines 5-29. As noted above, this issue is further complicated by the fact that it is not known what level, if any, of chloride ion transport will result in correction of the sodium ion transport defect, which may be more important in the pathology of the disease. See Alton and Geddes (1997) and Davies (1998), above. It is further noted that the rabbits used in these assays were normal, see page 73, line 23, and thus did not suffer from the accumulation of mucus associated with the CF in humans, which impedes vector access to the epithelium according to Rosenecker (1998, see page 152, column 2, lines 1-15 of second full paragraph). See also Davies (1998) page 292, column 2, lines 7-9 of first paragraph. For this reason, one of skill in the art could not reproduce in a CF patient the level of gene transfer observed in the rabbit model of the working example. Thus, even if one accepts that 6-10% transfection of epithelial cells is sufficient for treatment of CF, the instant specification has failed to teach how to achieve this level of transfection in a CF patient.

It is also noted that the scope of membrane channels which may be used in the invention



Art Unit: 1635

is not limited to CFTR but encompasses all membrane channels. Even if the specification taught how to use the CFTR membrane channel to treat CF, which it does not, the specification does not teach how to use any other membrane channel in the treatment of CF. The CFTR polypeptide is a chloride ion transporter which appears to be regulated by phosphorylation. See Rosenecker (1998, page 149, column 2, lines 11-14). One of skill in the art would not expect that a membrane channel designed for transport of other ions could be used to treat the disease, and the specification offers no guidance in this regard. For example, the specification fails to teach how to use the FOF1-ATPase/synthase, which comprises a membrane channel for hydrogen ions, in the treatment of CF. Furthermore, the specification fails to teach any example of a membrane channel that responds to the same regulatory signals as CFTR and in the same ways. Thus the specification has failed to teach how to restore appropriate cellular function using membrane channels other than CFTR, and one of skill in the art could not treat CF with such channels without undue experimentation.

In summary, while the specification teaches how to improve retrovirus infection of epithelial cells in vivo, it fails to teach how to use the claimed methods and compositions for the purpose intended by the specification, i.e. gene therapy of CF. The specification fails to add to the teachings of the prior art with respect to the identification of the type of cells which must be transfected, the number of cells which must be transfected, or the level of expression which is required in order to treat CF. It fails to teach whether or not CF can be treated by restoring only

Art Unit: 1635

chloride ion transport, or if restoration of the sodium ion defect is required. It also fails to teach how to achieve correction of the sodium ion defect. Finally it fails to teach how to transfect the minimum number of cells which the prior art suggests will be required to treat CF. Furthermore, gene therapy of CF is highly unpredictable because the prior art had established that both the target cells for treatment, and the nature of the defect which required correction were unknown.

Because the prior art teaches that it is not known which cells must be transfected with CFTR expression vectors in order to treat CF, how many of these cells must be transfected, or what level of expression must be obtained to effect treatment; because the instant invention provides transfection of a lower percentage of cells than the minimum which is deemed necessary by those of skill in the art to correct the CF chloride ion transport defect; because it is unknown if correction of the chloride ion transport defect will result in any therapeutic effect; and because the specification fails to provide the requisite teachings missing from the prior art, one of skill in the art would have to perform undue experimentation in order to use the invention as intended.

### ***Response to Arguments***

Applicant's arguments filed 3/18/02 have been fully considered but they are not persuasive.

Applicant argues at page 5 of the response that the assessment of the state of the art provided in the Office Action does not accurately represent the views of those of skill in the art.

Art Unit: 1635

This argument is supported by a single reference published after the date of filing, Crystal (1999). Applicant is reminded that developments occurring after the filing date of an application are of no significance regarding what one skilled in the art believed as of that filing date. See for example, *in re Wright*, 27 USPQ2d 1510, 1514 (Fed. Cir. 1993). In any event the Examiner supported his position with nine pertinent references published both before and after the time of filing, and Applicant has failed to point out specifically why any teachings of Crystal should be given more weight than those cited in the rejection

Applicant agrees at page 5 of the response that there is controversy over which target cells must be transfected in the lung in order to treat CF, and admits in the paragraph bridging pages 6 and 7, that there is no universal agreement as to the role of submucosal glands in CF. However, Applicant argues at page 6, top, that what is required for CF treatment is the restoration of chloride conductance by CFTR, and asserts at page 6, first full paragraph, that they have achieved chloride transport correction in vitro for 11 months after transduction with retroviral vectors. However, this assertion is not supported by evidence in a proper declaration under 37 CFR 1.132, and so it constitutes only hearsay and cannot be considered to be evidence of enablement. In any case, expression for 11 months in vitro is not the same thing as expression for 11 months in vivo. Because these results were obtained in vitro, not in vivo, they fail to address issues such as the transient expression commonly observed with retroviral vectors in vivo. See e.g. Crystal (J. Clin. Invest. 104(11): 1491-1493 (1999) of record, especially page 1492, last 11 lines of column 2). Furthermore, and as noted in the rejection, it is not clear what level of chloride ion transport will

Art Unit: 1635

be sufficient for treatment. Davies (1998) teaches that if normalization of sodium ion transport is required for therapeutic effect, then the levels of gene transfer observed to date will be inadequate because correction of sodium ion transport has not been achieved in the majority of preclinical and clinical studies. See page 294, column 2, lines 22-28. Also, Boucher indicates that it is likely that the number of gap junctions in vivo is less than that in the in vitro monolayer model, so the minimum number of cells which must be transfected in vivo may well exceed 10%. See page 442, column 1, lines 5-29.

Applicant appears to argue at page 7 that the identity of the target cells is either unimportant, or that transfection of surface epithelia, rather than submucosal glands, should be sufficient for therapy. Applicant relies for support on Zhou et al, who teach transgenic mice, null for mouse CFTR (mCFTR), but carrying one or more human CFTR (hCFTR) alleles expressed in intestinal surface epithelium. Mice lacking mCFTR generally die by the age of 40 days due to intestinal obstruction. Crosses of these null mice with mice transgenic for hCFTR alleles driven by an intestine-specific promoter resulted in increased longevity of mCFTR null mice. Applicant notes that expression of the transgene was not detected in the crypt epithelium, where mCFTR is normally expressed in the mouse, but was observed instead in the surface epithelium. The conclusion is that expression of CFTR in the surface epithelium of a transgenic animal is sufficient to correct the defect in CFTR. In response, the PTO notes that there is no evidence that the instant invention can be used to obtain the extent of gene expression found in a transgenic animal. The animals of Zhou contained a hCFTR allele in every cell, and it is

Art Unit: 1635

reasonable to expect that these animals contained hCFTR protein in all cells in which the transgene promoter was active. Furthermore, the gene was available for expression throughout the life of the animal. This could explain why the chloride transport rate observed in the hybrid mice was sufficient to prevent intestinal obstruction. See Zhou, page 1708, column 2, lines 5-11. It is not at all clear that Applicant's invention could be used to provide similar levels of gene expression in a similar amount of affected tissue. So, it is not clear that Applicant's invention could be used to treat CF by transfection of surface epithelium only.

In the paragraph bridging pages 7 and 8, Applicant argues that the existence of gaps in the knowledge of CF treatment does not preclude enablement, citing *In re Krimmel* for support. The PTO agrees, but notes that the gaps in knowledge that are pointed out in the rejection show that treatment of CF by gene therapy is extremely unpredictable.

At page 8, Applicant asserts that the hypothesis of Boucher regarding a possible required therapeutic transfection efficiency of greater than 10% is not accepted as a fundamental issue facing CF therapy. This assertion is unsupported by evidence. Applicant also notes that the inventors' own publication shows up to 14% transduction of tracheal epithelia in vivo (Wang et al 1999) and up to 10% transduction of epithelia in small airways (Wang et al 2000). Perusal of Wang (1999) shows that although regions comprising up to 14% transfected cells were seen, the average transfection reported was 4.8% +/- 5.6%. See lines 14-16 of paragraph bridging pages R58 and R59. As noted above, this amount falls short of the estimated 6-10% transfection efficiency required for treatment, even assuming that correction of sodium ion transport is not

Art Unit: 1635

important. Applicant failed to point to any passage in Wang (2000) which discloses 10% transduction, and the Examiner was unable to find any evidence to support this assertion.

Finally, Applicant argues at page 9 of the response, that application of therapy to infants and young children prior to the accumulation of mucus will overcome the barrier that mucus represents to transfection. This is unpersuasive because Applicant has failed to present any evidence that infants and children with CF have amounts of mucus which are not inhibitory to gene delivery. Furthermore Applicant has failed to consider the effects of surface fluid and cilia on transfection. See Rosenecker (1998), above.

For these reasons the rejection is maintained.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 6-8, 26-31, and 48-52 stand rejected under 35 U.S.C. 102(b) as being anticipated by Halbert et al (Human Gene Therapy 7(15): 1871-1881, 10/1996), as evidenced by

Art Unit: 1635

Puchelle (*Acta Oto-Rhino-Laryng. Belg.* 54 (3): 263-270, 2000).

Halbert teaches a method of increasing the susceptibility to retroviral infection of rabbit tracheal cells in vivo. Rabbit tracheas were abraded by brushing, resulting in a wound which necessarily increases transepithelial permeability. Replication defective retroviral vectors were delivered to the sites of the wounds. Infection of wounded rabbit tracheas was increased relative to that observed in unwounded tracheas. The retroviruses expressed the enzyme human placental alkaline phosphatase. See last sentence of abstract; page 1872, column 2, lines 12-20; Fig. 1 on page 1873; page 1874, column 2, second full paragraph, and lines 1-4 of next paragraph and Fig. 4 on page 1878. See also paragraph bridging columns 1 and 2 on page 1878; and paragraph bridging pages 1874 and 1875.

Claims 7 and 8 are included in this rejection because, although Halbert increases cellular proliferation by wounding rather than by direct application of a proliferative factor, the act of wounding causes the subsequent release of proliferative factors from the wounded tissue. Puchelle teaches that wounded airway epithelium is regenerated in a process involving growth factors. Thus damaging airway epithelial cells results in the subsequent contacting of these cells by growth factors. In other words, the step of contacting epithelial cells with growth factors is inherent in the method steps taught by Halbert.

Claim 29 is included in the rejection because it recites "enzymes" as a species of polypeptide which can be expressed by the retrovirus, and Halbert teaches the enzyme human placental alkaline phosphatase.

Art Unit: 1635

Thus Halbert anticipates tile claims.

It is noted that even though Halbert is not considered to be enabling for therapeutic methods, the method steps of Halbert still read on the rejected claims. Even though the specification discloses no use for the claimed method other than gene therapy, the rejected claims do not recite a therapeutic outcome, thus the PTO is obligated to set forth the rejection because the prior art teaches the same method steps as the claims.

### ***Response to Arguments***

Applicant's arguments filed 3/18/02 have been fully considered but they are not persuasive. Applicant argues at page 11 of the response that the claims as amended are distinguished from the methods of Halbert because the claims require that the composition must comprise a tissue permeabilizing agent. This is unpersuasive, because the brush of Halbert can be considered to be the tissue permeabilizing agent.

### ***Conclusion***

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO



Art Unit: 1635

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.



JAMES KETTER  
PRIMARY EXAMINER